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CED-SOS Advice Report 4 EDUCATION AND INFORMATION 2012

The Role of Liposomal Doxorubicin in the Treatment of Metastatic Breast Cancer

S. Dent, R.B. Rumble, T. Vandenberg, M. Clemons, and H. Messersmith

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 10, 2007

This DQTC-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
The report, which consists of a Summary and a Full Report, is available on the CCO web site (http://www.cancercare.on.ca).

A CED-SOS Advice Report is a document developed by the PEBC in response to a request from the Committee to Evaluate Drugs (CED) for a review of the clinical evidence on a specific cancer drug or combination of drugs. An abbreviated systematic review of the literature is undertaken in a very short time period.
This particular document was developed by one clinical expert and one PEBC staff member. This document has been internally approved by PEBC management but has not been subject to a broader external review due to time constraints.

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The 2007 guideline recommendation was put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

Report Date: May 10, 2007

SUMMARY

Questions

1. What is the role of liposomal doxorubicin in the treatment of metastatic breast cancer?
2. What is the role of liposomal doxorubicin in combination with trastuzumab in the first-line treatment of metastatic breast cancer?

The main outcome of interest for both questions is cardiotoxicity (e.g., left ventricular ejection fraction reduction, congestive heart failure). Secondary outcomes of interest were response rates and time to progression.

Target Population

These recommendations apply to adult female patients with metastatic breast cancer suitable for first-line treatment.

Recommendation and Key Evidence

Women with metastatic breast cancer who would normally be considered for single-agent anthracycline therapy or anthracycline/cyclophosphamide combination therapy could be considered for liposomal doxorubicin, alone or in combination with

cyclophosphamide. See Full Report, Appendix 1 for possible regimens and dosages.

Left Ventricular Ejection Fraction

- Three randomized controlled trials (RCTs), involving a total of 1,030 patients, detected statistically significant differences in left ventricular ejection fraction (LVEF) between liposomal doxorubicin (alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide) in favour of liposomal doxorubicin.
- One RCT comparing liposomal doxorubicin plus cyclophosphamide versus epirubicin plus cyclophosphamide that involved 160 patients did not detect a statistically significant difference in LVEF between treatment arms.

Congestive Heart Failure

- Two RCTs, involving a total of 521 patients, detected statistically significant differences in congestive heart failure (CHF) rates favouring treatment with liposomal doxorubicin (alone and in combination with cyclophosphamide) compared with doxorubicin (alone or in combination with cyclophosphamide).
- Two RCTs, involving 669 patients, did not detect a statistically significant difference in CHF rates between treatment arms.

Response Rates

- Four RCTs, involving a total of 1,190 patients, found no statistically significant differences in response rates between liposomal doxorubicin (alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide).

Time to Progression

- Three RCTs, involving a total of 1,030 patients, did not find any statistically significant differences in time to progression between liposomal doxorubicin (alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide).
- One RCT, involving 160 patients and comparing liposomal doxorubicin plus cyclophosphamide versus epirubicin plus cyclophosphamide, detected a statistically significant difference in time to progression in favour of treatment with liposomal doxorubicin.

Qualifying Statements

- There is currently no randomized evidence to support the concurrent administration of liposomal doxorubicin and trastuzumab in women with HER2 over-expressing metastatic breast cancer.
- While one might consider liposomal doxorubicin use in women at an increased risk of cardiotoxicity because of pre-existing cardiac disease or prior anthracycline use, these women were not, by and large, included in the trials to date, and the advantage of liposomal doxorubicin in these women is still unknown.

Future Research

Women with HER2 over-expressing metastatic breast cancer may benefit from the administration of anthracycline-containing trastuzumab combination therapy; however, the utility of these regimens has been hampered by the significant increase in cardiotoxicity. Future research should focus on establishing the efficacy and safety of liposomal doxorubicin-

containing trastuzumab combinations in this population. Additionally, confirmation women with prior anthracycline exposure, or at high risk for cardiotoxicity will also experience the reduced toxicity found in the identified trials is needed.

Please see the Full Report, Appendix 3 for a listing of relevant on-going trials.

Related Guidelines

Practice Guideline 1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer*.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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FULL REPORT

I. QUESTIONS

1. What is the role of liposomal doxorubicin in the treatment of metastatic breast cancer?
2. What is the role of liposomal doxorubicin in combination with trastuzumab in the first-line treatment of metastatic breast cancer?

The main outcome of interest for both questions is cardiotoxicity (e.g., left ventricular ejection fraction reduction, congestive heart failure). Secondary outcomes of interest were response rates and time to progression.

II. CHOICE OF TOPIC AND RATIONALE

Breast cancer is the most common cancer in women (1). Current estimates suggest that there are 141,000 breast cancer patients in Canada, and breast cancer is responsible for 91,000 potential years of life lost each year (1). In 2003, there were 21,200 new cases of breast cancer diagnosed and 5,300 deaths from breast cancer in Canada (2). The Early Breast Cancer Trialists Collaborative Group overview (3) demonstrated a survival benefit for women with early-stage breast cancer treated with adjuvant polychemotherapy; however, 40% of patients developed recurrent and/or metastatic disease.

Anthracyclines (e.g., epirubicin, doxorubicin) used either alone or in combination with other chemotherapeutic agents are among the most active therapies for the treatment of metastatic breast cancer (MBC) (3). The clinical utility of anthracyclines is limited in part by their potential for cardiotoxicity (e.g. cardiomyopathy, congestive heart failure) (4). The incidence of clinically significant cardiotoxicity rises with increasing lifetime doses of these drugs; doses greater than 450 mg/m^2 with doxorubicin, and doses greater than 900 mg/m^2 with epirubicin (5). Sub-clinical (and occasionally overt) cardiotoxicity may also occur at lower cumulative doses of anthracyclines, especially when the drug is given as part of a combination regimen or with newer biologic therapies (e.g., trastuzumab). An average three-fold greater cardiac toxicity effect was seen in women that received the combination of trastuzumab, an anthracycline (either doxorubicin or epirubicin), and cyclophosphamide (AFC), compared with the rates of cardiotoxicity that would have been expected with an anthracycline and cyclophosphamide (AC) or with trastuzumab alone (6). The same clinical trials also suggested that, despite the high rates of cardiac toxicity, the combination of anthracyclines with trastuzumab (and cyclophosphamide) might be more efficacious (improved time to progression, overall survival) in MBC compared to non-anthracycline containing trastuzumab regimens (6). An anthracycline formulation with comparable efficacy and improved safety would increase the drug's therapeutic index and enhance its overall clinical benefit.

The liposomal encapsulation of anthracyclines, particularly doxorubicin, has the potential to decrease the toxicity of these agents. Intravenously injected liposomes cannot escape the vascular space in sites that have tight capillary junctions, such as the heart muscle (7). The liposomes generally exit the circulation into tissues and/or areas where capillaries are disrupted by inflammation or tumour growth (8). Preclinical studies have demonstrated that liposomal doxorubicin reduces the peak distribution of doxorubicin to the heart but delivers doxorubicin effectively to tumours (9). Early animal studies found reduced cardiotoxicity effects with the liposomal formulation (10).

With the availability of RCTs, a systematic review of the evidence for the use of liposomal doxorubicin in women with MBC is warranted.

III. METHODS

This advice report was developed by the Program in Evidence-based Care (PEBC) following a request from the Committee to Evaluate Drugs (CED). PEBC staff worked with three clinical experts to develop an abbreviated systematic review and clinical recommendations. This topic was not developed by the PEBC's Breast Cancer Disease Site Group, although the three clinical experts are members of this committee. This document has undergone formal internal approval by the PEBC but has not been formally reviewed by the Breast Cancer Disease Site Group or external clinicians in Ontario at this time.

This advice report, produced by the PEBC, is a convenient and up-to-date source of the best available evidence on the role of liposomal doxorubicin in the treatment of MBC developed through systematic reviews of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

The MEDLINE (January 1996 through July week one 2006), EMBASE (Week one 1996 through week 28 2006), and Cochrane database of systematic reviews (through Issue 2, 2006) were searched for relevant evidence. The search terms used are shown in Table 1. Additionally, the conference proceedings from the 2003-2006 meetings of the American Society of Clinical Oncology were searched for abstracts of relevant trials.

Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from those sources were searched for additional trials.

Table 1. Literature search strategy.

Search date	Database	Search terms used
July 18, 2006	MEDLINE	Doxorubicin [MeSH], liposomal doxorubicin [MeSH], breast neoplasms [MeSH], randomized controlled trials [MeSH], trastuzumab
July 18, 2006	EMBASE	Liposomal doxorubicin, trastuzumab, breast cancer
July 18, 2006	Cochrane dB of Systematic Reviews	Breast cancer
July 18, 2006	ASCO Abstracts	Liposomal doxorubicin, breast cancer

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports or published abstracts involving human subjects of randomized controlled trials (RCTs) comparing liposomal doxorubicin with other anthracyclines with or without trastuzumab that reported cardiotoxicity effects.

Exclusion Criteria

1. Letters and editorials were not eligible.
2. Phase II trials were not eligible

Synthesizing the Evidence

Due to heterogeneity of regimens used and outcomes reported on, data were not pooled using meta-analytic techniques.

IV. RESULTS

Literature Search Results

The MEDLINE search yielded 20 hits, seven of which were potentially relevant, and were ordered for full-text review. The EMBASE search yielded 21 hits, 19 of which were ordered for full-text review, the Cochrane dB search yielded 5 hits, which were all ordered for full-text review, and the ASCO abstracts search yielded 22 potentially relevant reports (Table 2).

Table 2. Literature search results

Date	Database	Database searched up to	Hits	Ordered for full article review
July 18, 2006	MEDLINE	July (week one) 2006	20	7
July 18, 2006	EMBASE	Through week 28 2006	21	19
July 18, 2006	Cochrane dB of Systematic Reviews	Issue 2, 2006	5	5
July 18, 2006	ASCO Abstracts	2006 Annual Meeting	N/A	22

Of the articles ordered for full review, only two (11,12) were considered relevant and were retained for data extraction. Two additional RCTs (13,14) that were not found in the literature search but that did meet the inclusion criteria were forwarded by one of the authors (SD). All four of the RCTs obtained reported pharmaceutical industry sponsorship, three by Elan Pharmaceuticals (11,13,14) and the other by Schering-Plough Research Institute (12). See Table 3 for trial outcomes and Table 4 for cardiac toxicity definitions by trial. There were no reported phase III randomized trials of liposomal doxorubicin in combination with trastuzumab versus non-liposomal doxorubicin and trastuzumab.

Outcomes

Four RCTs involving 1,190 patients were obtained (11-14). Three of the four trials (12-14) detected a statistically significant difference ($p<0.05$) for LVEF in favour of liposomal doxorubicin over their comparator arms (doxorubicin plus cyclophosphamide, and doxorubicin alone (two trials)). Two of the four trials (13,14) detected a statistically significant difference ($p<0.05$) for CHF in favour of liposomal doxorubicin over their comparator arms (doxorubicin plus cyclophosphamide, and doxorubicin alone). None of the trials detected any statistically significant differences between the groups for response rates or median time to progression with the exception of the trial by Chan et al (11) that detected a statistically significant difference in median TTP in favour of non-pegylated liposomal doxorubicin plus cyclophosphamides over epirubicin plus cyclophosphamides ($p=0.02$). See Table 3 for outcomes. All of the included trials excluded patients with previous serious cardiac problems, such as congestive heart failure and arrhythmia. For those trials that allowed it (all but Harris et al), the proportion of patients with previous anthracycline exposure ranged from 10% to 18% by arm. See Appendix 2 for a summary of the patient characteristics of the included trials.

The first RCT, reported by Batist et al (13), compared liposome-encapsulated doxorubicin plus cyclophosphamide with conventional doxorubicin plus cyclophosphamide in 297 females with MBC. No statistically significant differences were detected between treatments for response rates or time to progression; however, a statistically significant difference was detected between arms for both LVEF and CHF in favour of treatment with liposome-encapsulated doxorubicin (LVEF, 9 versus 28, $p=0.0001$; CHF, 0 versus 5, $p=0.02$).

The second RCT, reported by Harris et al (14) compared liposome-encapsulated doxorubicin with conventional doxorubicin in 224 females with MBC. No statistically

significant differences were detected between treatments for response rates or time to progression; however, a statistically significant difference was detected between arms for both LVEF and CHF in favour of treatment with liposome-encapsulated doxorubicin (LVEF, 12 versus 25, p=0.008; CHF, 2 versus 9, p=0.0001).

The third RCT, reported by Chan et al (11) compared liposome-encapsulated doxorubicin plus cyclophosphamide with epirubicin plus cyclophosphamide in 160 anthracycline-naïve MBC patients. No statistically significant differences in cardiotoxicity effects or response rates were detected between the two treatments; however, the liposomal doxorubicin arm demonstrated superior time to progression (7.7 months versus 5.6 months; p=0.02).

The fourth RCT, reported by O'Brien et al (12) compared pegylated liposomal doxorubicin with conventional doxorubicin in 509 female patients with locally advanced or MBC (stage IIIB or IV). Patients were allowed to have received prior hormonal or adjuvant anthracycline therapy if the cumulative doxorubicin (or equivalent) dose did not exceed 300 mg/m^2 and the chemotherapy-free interval exceeded 12 months. No statistically significant differences were detected between treatments for response rates or time to progression; however, a statistically significant difference was detected between arms for cardiotoxicity (LVEF) in favour of liposomal doxorubicin (10 patients versus 48 patients; p<0.001).

Table 3. Treatment outcomes by study.

Study author, (reference), [location], protocol ID, year	Comparison	Number of patients	Cardiotoxicity effects (N)		RR [CR+PR] (%)	Median TTP (months)
			LVEF	CHF		
Batist G et al (13) [Canada/ US] 2001	LED+CP	142	6% (9)	0% (0)	43	5.1
	D+CP	155	18% (28) p=0.0001	3% (5) p=0.02	43 p=ns	5.5 p=ns
Harris L et al (14) [Canada/ US] 2002	LED	108	11% (12)	2% (2)	[0+26] 26	3.8
	D	116	22% (25) p=0.008	8% (9) p=0.0001	[2+24] 26 p=ns	4.3 p=ns
Chan S et al (11) [UK] 2004	LED+CP	80	11% (9)	0% (0)	46	7.7
	E+CP	80	10% (8) p=ns	0% (0) p=ns	39 p=ns	5.6 p=0.02
O'Brien MER et al (12) [UK] 2004	PLD	254	4% (10)	1% (2)	33	7.3
	D	255	19% (48) p<0.001, HR=3.16	1% (2) p=ns	38 p=ns	7.1 p=ns

Note: N, number; RR, response rate; TTP, time to progression; LED, liposome-encapsulated doxorubicin; CP, cyclophosphamide; D, doxorubicin; LVEF, left ventricular ejection fraction; CHF, congestive heart failure;; E, epirubicin; PLD, pegylated liposomal doxorubicin; ns, not significant.

Table 4. Definitions of cardiotoxicity by trial.

Batist G et al (2001) Defined as a decrease in resting LVEF of ≥ 20 ejection fraction (EF) units from baseline to a final value of ≥ 50%, or a decrease of ≥ 10 EF units from baseline to a final value of less than 50%, or clinical evidence of CHF.
Harris L et al (2002) Defined as a decrease in resting LVEF of 20 or more points from baseline to a final value of greater than or equal to 50%, a decrease of greater than or equal to 10 points from baseline to a final value of less than 50%, a cardiac biopsy of Grade 2.5 or higher, or clinical evidence of CHF.
Chan S et al (2004) Defined as a decrease in resting LVEF of ≥ 20 units from baseline to a final value of ≥ 50%, or a decrease of ≥ 10 units from baseline to ≥ 50%, or clinical evidence of CHF.
O'Brien MER et al (2004) Defined as a decrease of ≥ 20% from baseline if the resting LVEF remained in the normal range or a decrease of ≥ 10% if the LVEF became abnormal (less than the institutional lower limit of normal). A diagnosis of CHF required the presence of signs and symptoms requiring treatment specific for CHF (e.g. dyspnea upon exertion, peripheral edema, orthopnea, or tachypnea).

V. INTERPRETIVE SUMMARY

Anthracyclines, used alone or in combination, remain one of the most effective therapies used in the treatment of MBC. Their clinical utility has been hampered by their potential for clinically significant cardiac toxicity. Four phase III randomized control trials comparing liposomal doxorubicin with conventional anthracycline, demonstrated similar anti-tumour activity, with one trial (11) demonstrating longer time to progression with liposomal doxorubicin. Three of the four trials reported a significant reduction in cardiotoxicity (as measured by changes in LVEF or clinical evidence of CHF) with the liposomal doxorubicin preparation. The fourth trial (11) showed no significant differences in cardiotoxicity between the two doxorubicin arms; however, this trial was the smallest and may have been underpowered.

Given the reduced toxicity and proven efficacy, liposomal doxorubicin could be considered a treatment option in women would normally receive single-agent anthracycline (epirubicin or doxorubicin) or anthracycline plus cyclophosphamide. While one might consider liposomal doxorubicin use in women at an increased risk of cardiotoxicity because of pre-existing cardiac disease or prior anthracycline use, these women were not, by and large, included in the trials to date and the advantage of liposomal doxorubicin in these women is still unknown.

There are no trials at this time that compare liposome-encapsulated doxorubicin with pegylated liposomal doxorubicin. Therefore, at this time there is no evidence with which to evaluate the relative benefits or harms of either formulation compared to the other.

VI. RECOMMENDATIONS AND EVIDENCE

Recommendation and Key Evidence

Women with metastatic breast cancer who would normally be considered for single-agent anthracycline therapy or anthracycline/cyclophosphamide combination therapy could be considered for liposomal doxorubicin, alone or in combination with cyclophosphamide. See Appendix 1 for possible regimens and dosages.
Left Ventricular Ejection Fraction • Three RCTs, involving a total of 1,030 patients, detected statistically significant differences in left ventricular ejection fraction (LVEF) between liposomal doxorubicin

(alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide) in favour of liposomal doxorubicin.
- One RCT comparing liposomal doxorubicin plus cyclophosphamide versus epirubicin plus cyclophosphamide that involved 160 patients did not detect a statistically significant difference in LVEF between treatment arms.

Congestive Heart Failure
- Two RCTs, involving a total of 521 patients, detected statistically significant differences in congestive heart failure (CHF) rates favouring treatment with liposomal doxorubicin (alone and in combination with cyclophosphamide) compared with doxorubicin (alone or in combination with cyclophosphamide).
- Two RCTs, involving 669 patients, did not detect a statistically significant difference in CHF rates between treatment arms.

Response Rates
- Four RCTs, involving a total of 1,190 patients, found no statistically significant differences in response rates between liposomal doxorubicin (alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide).

Time to Progression
- Three RCTs, involving a total of 1,030 patients, did not find any statistically significant differences in time to progression between liposomal doxorubicin (alone or in combination with cyclophosphamide) and doxorubicin or epirubicin (alone or in combination with cyclophosphamide).
- One RCT, involving 160 patients, comparing liposomal doxorubicin plus cyclophosphamide versus epirubicin plus cyclophosphamide detected a statistically significant difference in time to progression in favour of treatment with liposomal doxorubicin.

Qualifying Statement
- There is currently no evidence to support the concurrent administration of liposomal doxorubicin and trastuzumab in women with HER2 over-expressing metastatic breast cancer.
- While one might consider liposomal doxorubicin use in women at an increased risk of cardiotoxicity because of pre-existing cardiac disease or prior anthracycline use, these women were not, by and large, included in the trials to date and the advantage of liposomal doxorubicin in these women is still unknown.

Future Research

Women with HER2 over-expressing MBC may benefit from the administration of anthracycline-containing trastuzumab combination therapy; however, the utility of these regimens has been hampered by the significant increase in cardiotoxicity. Future research should focus on establishing the efficacy and safety of liposomal doxorubicin-containing trastuzumab combinations in this population. Additionally, confirmation women with prior anthracycline exposure, or at high risk for cardiotoxicity will also experience the reduced toxicity found in the identified trials is needed.

See Appendix 3 for a listing of relevant on-going trials.

Related Guidelines

Practice Guideline 1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer*.

VII. CONFLICTS OF INTEREST

The authors of this report declared that there were no potential conflicts of interest related to the topic of this CED-SOS advice report.

VIII. ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. Susan Dent, Mr. R.B. Rumble, Dr. Ted Vandenberg, and Dr. Mark Clemons for taking the lead in drafting and revising this CED-SOS advice report.

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Appendix 1. Dosing by trial.

Regimens by trial
Batist G et al (2001) Liposome-encapsulated doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2 *versus* Doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2
Harris L et al (2002) Liposome-encapsulated doxorubicin 75 mg/m^2 *versus* Doxorubicin 75 mg/m^2
Chan S et al (2004) Liposome-encapsulated doxorubicin 75 mg/m^2 1 hour IV infusion plus cyclophosphamide 600 mg/m^2 15 minute IV infusion, repeated every three weeks for up to eight cycles *versus* Epirubicin 75 mg/m^2 1 hour IV infusion plus cyclophosphamide 600 mg/m^2 15 minute IV infusion, repeated every three weeks for up to eight cycles
O'Brien MER et al (2004) Pegylated liposomal doxorubicin 50 mg/m2 1 hour IV infusion every four weeks, repeated until disease progression *versus* Doxorubicin 60 mg/m2 1 hour IV infusion every three weeks, repeated until disease progression

Appendix 2. Patient characteristics from the included trials.

Batist G et al (2001)
• Age 18 and older • histologically confirmed, bi-dimensionally measurable metastatic breast cancer • ECOG PS ≥ 2 • adequate bone marrow function (WBC count ≥ 3.5 * 10^9/L, neutrophil count ≥ 2.0 * 10^9/L, hemoglobin ≥ 10 g/dL, platelet count ≥ 100 * 10^9/L) • adequate liver function (≤ 1.2 times the upper normal limit for bilirubin and ≤ four times the upper normal limit for AST and ALT) • adequate renal function (serum creatinine < 1.5 mg/dL) • all patients were required to have a resting left ventricular ejection fraction (LVEF) ≥ 50% • no documented history of congestive heart failure (CHF), serious arrhythmia, or myocardial infarction (within 6 months) • adjuvant CT, including doxorubicin if the total cumulative dose did not exceed 300 mg/m^2, was allowed if more than 6 months had elapsed
Harris L et al (2002)
• Age 18 or older • histologically or cytologically proven breast carcinoma with measurable metastatic disease • ECOG PS 0-2 • life expectancy of at least 3 months • adequate bone marrow function (leukocyte count of ≥ 3500 cells/μL, absolute neutrophil counts ≥ 2000 cells/μL, platelets ≥ 100,000 cells/μL) • adequate liver function (serum bilirubin ≤ 1.2 times the upper limit of normal) • adequate renal function (< 1.5 mg/dL) • LVEF ≥ 50%, no history of CHF, serious cardiac arrhythmia, or myocardial infarction • adjuvant doxorubicin up to a lifetime maximum dose of 300 mg/m^2 was allowed, but patients should not have received adjuvant treatment with other anthracyclines or anthracenediones • patients could not have received CT for metastatic disease or adjuvant CT within 6 months of entering the study
Chan S et al (2004)
• Age ≥ 18 • histologically or cytologically proven breast carcinoma with measurable metastatic disease • ECOG PS ≥ 2 • life expectancy of ≥ 3 months • adequate bone marrow, liver, and renal function • a resting LVEF ≥ 50% • Patients were ineligible if they had received previous anthracyclines or other cytotoxic CT for metastatic disease, or if they had received adjuvant CT within the past 6 months. • patients with a history of cardiac problems were excluded for safety reasons
O'Brien MER et al (2004)
• Age ≥ 18 • WHO PS ≤ 2 • measurable or evaluable Stage IIIB or IV metastatic breast cancer • normal hematological, hepatic, renal, and cardiac (LVEF within normal limits) function was required • no history of ischemic heart disease, arrhythmia requiring treatment, or clinically significant valvular disease • patients with elevated bilirubin concentration and/or elevated alanine aminotransferase/aspartate aminotransferase were eligible for inclusion if reduced liver function was secondary to liver metastases • prior hormonal or adjuvant anthracycline therapy was permitted with a cumulative doxorubicin (or dox equivalent) dose of ≤ 300 mg/m^2, and CT-free interval of > 12 months

Appendix 3. Ongoing trials.

A study of docetaxel monotherapy or DOXIL®/CAELYX® and docetaxel in patients with advanced breast cancer.	
Protocol ID:	DOXIL-BCA-3001; NCT00091442
Date last verified:	June 15, 2006
Type of trial:	Phase III RCT
Accrual:	NR
Sponsorship:	Johnson & Johnson Pharmaceutical Research & Development, LLC
Status:	Open and recruiting
Phase III randomized study of adjuvant pegylated doxorubicin hydrochloride liposome (PDL) versus observation or PDL versus low-dose cyclophosphamide and methotrexate in elderly women with resected, hormone receptor-negative breast cancer.	
Protocol ID:	IBCSG-32-05; BIG-1-05; BIG-CASA; EU-205112; EUDRACT-2005-003434-18; NCT00296010
Date last verified:	March 30, 2006
Type of trial:	Phase III RCT
Accrual:	1,296
Sponsorship:	International Breast Cancer Study Group
Status:	Open and recruiting